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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,176	11/24/2003	Tariq M. Rana	UMY-059	3047

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LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/722,176	RANA, TARIQ M.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14 and 17-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14, 17-34, 38-42* is/are rejected.

7)☒ Claim(s) *17,18 and 35-37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 11/25/2005 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 08/23/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 11/25/2005, claims 14, 17-34 and 38-42 are pending in the application. Applicant has canceled claims 1-13, and 15-16.

Claim Objections

Claims 35-37 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and/or cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 35-37 have not been further treated on the merits.

Claims 17 and 18 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Independent claim 14 is drawn to a delivery mixture comprising a dendrimer and a nucleic acid capable of mediating RNAi. Claims 17 and 18 fail to further limit claim 14 because the claims recite the nucleic acid further comprises a nucleotide sequence that encodes a RNA precursor that is now capable of mediating RNAi when the nucleic acid in claim 14 is already capable of mediating RNAi.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 14, 19-20, 23-24 and 33-34 are rejected under 35 U.S.C. 102(e) as being anticipated by Woolf (US 2006/0009409).

The instant claims are drawn to a delivery mixture comprising a dendrimer and a nucleic acid capable of mediating RNAi wherein the nucleic acid is an RNA molecule, wherein the RNA

is a siRNA, wherein the siRNA is from 16-30, 23-32 or 21 nucleotides in length and wherein the siRNA comprises a sense and antisense strand complementary to a target mRNA sequence.

Woolf teach a delivery complex comprising a PAMAM complex (see paragraph 0203) and a double stranded RNA (see paragraphs 0048-0050). Woolf teach the dsRNA is between 18 and 29 nucleotides in length (see paragraph 0071) and wherein the dsRNA comprises a sense and antisense strand complementary to a target mRNA sequence (see paragraph 0176).

Thus, Woolf et al. anticipates claims 14, 19-20, 23-24 and 33-34.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14, 19-20, 23-24 and 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woolf (US 2006/0009409) in view of Olejnik et al. (Nucleic Acids Research, 1996) in view of Grigoriev et al. (PNAS 1993).

Woolf teach a delivery complex comprising a PAMAM complex (see paragraph 0203) and a double stranded RNA (see paragraphs 0048-0050). Woolf teach the dsRNA is between 18 and 29 nucleotides in length (see paragraph 0071) and wherein the dsRNA comprises a sense and antisense strand complementary to a target mRNA sequence (see paragraph 0176). Woolf teaches modifications comprising conjugates and detectable moieties linked to the 3' terminus of the double stranded RNA (see paragraph 0096 and 0109-0110). Woolf does not teach dsRNA

comprising photocleavable biotin modifications and does not teach double stranded RNA containing psoralen crosslinks.

Olejnik et al. teach oligonucleotides comprising photocleavable biotin (see page 362).

Grigoriev et al. teach incorporation of psoralens into oligonucleotide for formation of psoralen crosslinks (see Figure 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate modifications such as photocleavable biotin and crosslinks using psoralens, into the dsRNA.

One would have been motivated to incorporate a photocleavable biotin modification into the siRNA contained in the delivery mixture comprising a dendrimer because Olejnik et al. teach incorporation of a photocleavable biotin into a oligonucleotide provides a simple method for purification of oligonucleotides (see abstract). Additionally, Olejnik et al. teach incorporation of a photocleavable biotin allows isolation of nucleic acids after synthesis and after cleavage of the biotin moiety, the functional nucleic acids can be used in further methods (see page 361). Further, one would have been motivated to incorporate psoralens, as taught by Grigoriev et al., into the siRNA contained in the delivery mixture to increase the target specificity of the siRNA to the target gene once the siRNA is delivered to cells. Grigoriev et al. teach addition of psoralen derivatives to oligonucleotides increase the antisense target affinity and half-life by crosslinking the antisense oligonucleotide to the target (see page 3501).

One would have a reasonable expectation of success of incorporating a photocleavable biotin and psoralen crosslinks into the siRNA contained in the delivery mixture because Olejnik et al. teach synthesis of an oligonucleotide comprising a photocleavable biotin and teach efficient

purification of the oligonucleotide and photocleavable of the biotin moiety and further Grigoriev et al. teach efficient inhibition of gene expression using cross linked nucleic acids.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 14, 17-24, 32-34 and 38-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoo et al. (PTO Form 892 filed 08/23/05) in view of Hammond et al. (Nature 2001, Vol. 2: 110-119), Tuschl et al. (WO 02/44321) and McManus et al. (Nature Review: Genetics 2002).

The instant claims are drawn to a delivery mixture comprising a dendrimer and a nucleic acid capable of mediating RNAi wherein the nucleic acid comprises an RNA precursor, wherein the nucleotide sequence that encodes an RNA precursor is operably linked to a polymerase III promoter, wherein the nucleic acid is an RNA molecule, wherein the RNA is a miRNA, a shRNA or a siRNA, wherein the siRNA comprises a sense and antisense strand complementary to a target mRNA sequence, wherein the sense and antisense strands are crosslinked, wherein the crosslink is psoralen, wherein the siRNA comprises a modification at the 3'OH terminus, wherein the modification is selected from group as listed in claim 29-30, wherein the dendrimer is PAMAM, wherein the siRNA is from 16-30, 23-32 or 21 nucleotides in length, wherein the PAMAM and siRNA are present at a PAMAM:siRNA ratio between 10-1 mg/100 pmol, 20-40 mg/100 pmol or 40 mg/ 100 pmol.

Yoo et al. teach a delivery mixture comprising a PAMAM dendrimer and an antisense nucleic acid capable of inhibiting gene expression (see page 1799 to 1800). Yoo et al. teach

various ratios of dendrimer to nucleic acid for optimization. Yoo et al. do not teach a dsRNA or a RNA precursor capable of mediating RNAi.

Hammond et al. teach two molecules used for silencing specific genes: antisense and dsRNA. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach ..."dsRNAs have been shown to inhibit gene expression in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression."

Tuschl et al. teach siRNA molecules, 19-23 nucleotides in length, that mediate RNAI and wherein the nucleotides of the sense strand and antisense strand are complementary to the target gene (see page 6, lines 8-15 and Figure 14).

McManus et al. teach shRNA and microRNA, which mediate RNAi (see page 740) and further teach a nucleic acid encoding a RNA precursor operably linked to a polymerase III promoter wherein the RNA precursor mediates RNAi (see figure 5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the delivery mixture comprising a dendrimer for delivering a dsRNA instead of an antisense molecule.

One would have been motivated to make a delivery mixture comprising a dendrimer and a siRNA instead of an antisense because Hammond et al. teach that siRNA are more efficient than antisense for probing gene function and for inhibiting gene expression. In probing gene function and inhibition of gene expression, one of skill in the art would be motivated to use the most efficient methodology and therefore one would have been motivated to use siRNA or

miRNA because Tuschl et al. and McManus et al. teach both siRNA and miRNA mediate RNAi efficiently in cells, thereby allowing elucidation of gene function. Because dsRNA is a nucleic acid, one would expect to encounter similar issues in delivery to cells as with antisense oligonucleotides and therefore one would be motivated to use a delivery mixture comprising a dendrimer because the goal for siRNA therapy is optimal delivery of the siRNA and enhanced cellular uptake by the cells. Yoo et al. teach a delivery mixture comprising a dendrimer provides advantages such as extended circulation lifetime, formation of stable complexes with oligonucleotides and increased concentration at the target site in the presence of serum; advantages that are not see in other commercially available delivery agents (see page 1999 and last paragraph page 1803). Additionally, Yoo et al. demonstrate the routine nature of testing various ratios of dendrimer to oligonucleotide, from 15 ug/ml to 90 ug/ml (see Figure 1 and Figure 2) for optimization of the most efficient ratio for delivery and gene inhibition and therefore because the use of dendrimers in a delivery mixture, as claimed by the instant invention, were known to add benefits to delivery of oligonucleotides molecules to cells, one would have been motivated to make a delivery mixture comprising siRNA and test various ranges for the optimal concentration.

Finally, one would have a reasonable expectation of success because Yoo et al. teach antisense nucleic acids molecules can be delivered to cells using a delivery mixture comprising a dendrimer and Hammond et al. teach that of the two molecules used to administer to cells for silencing gene function, dsRNA is more potent and sequence specific than antisense. One would have a reasonable expectation of success to make a delivery mixture comprising a dendrimer and a nucleic acid capable of mediating RNAi because Tuschl et al. and McManus et al. teach siRNA

and miRNA that efficiently mediated RNAi and further one would expect the nucleic acids taught by Yoo et al. and the nucleic acids taught by Tuschl et al. and McManus et al. to be similarly delivered using a mixture comprising a dendrimer.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicants Arguments

Claim Rejections - 35 USC § 103

Applicant argues that based on the teachings of Yoo et al. one would not be motivated to use alternative molecules to antisense for gene silencing and based on the teachings of Hammond et al., one would not be motivated to make a delivery mixture for delivering RNAi-mediating nucleic acids. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As explained in detail above, the combination of reference are relied upon to reject the instant claims because it would have been *prima facie* obvious for one of skill in the art to make a delivery mixture comprising a dendrimer and a nucleic acid capable of mediating RNAi since Yoo et al. teach an efficient delivery mixture comprising a dendrimer and a nucleic acid and Hammond et al. teach RNAi using siRNA is more specific methodology for gene silencing and finally Tuschl et al. and McManus et al. teach efficient gene silencing using a siRNA.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also

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Kimberly Chong
Examiner
Art Unit 1635

SEAN McGARRY
PRIMARY EXAMINER
1635